United States
Department of
Agriculture

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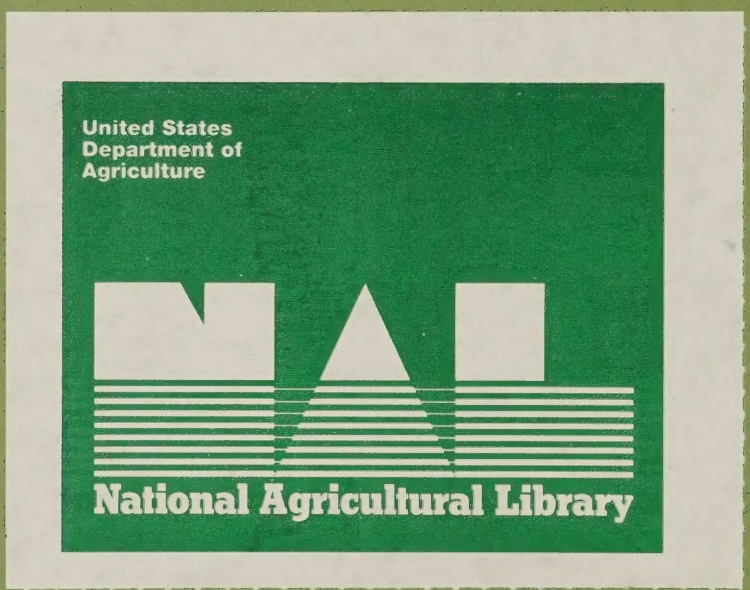
Minutes

Agricultural Biotechnology Research Advisory Committee

Confinement Working Group Meeting
November 11, 1988

Guidelines Working Group Meeting
December 2, 1988

Document No. 88-WG-04 and 05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U.S. DEPARTMENT OF AGRICULTURE
AGRICULTURAL BIOTECHNOLOGY RESEARCH ADVISORY COMMITTEE
CONFINEMENT WORKING GROUP MEETING
Congress Hotel, Chicago, Illinois

November 11, 1988

The meeting of the Agricultural Biotechnology Research Advisory Committee (ABRAC) Confinement Working Group was called to order on November 11, 1988 at 1:00 p.m. by Dr. John Gorham. This date was selected to take advantage of the expertise at the 41st Annual Brucellosis Research Conference held at the Congress Hotel on November 12-13, 1988. The meeting was open to the public and was announced in the Federal Register.

Other members of the Working Group in attendance were Manuel Barbeito, Agricultural Research Service (ARS), George Shibley, Animal and Plant Health Inspection Service (APHIS), Gerhardt Schurig, Virginia Polytechnic Institute and State University (VPI). The Office of Agricultural Biotechnology (OAB) was represented by Phillip O'Berry, Maryln Cordle, and Janet Herrick.

Others present were: Mark Sanborn, Oklahoma State University; John Mayfield, Iowa State University; Billy Deyoe, USDA/ARS, National Animal Disease Center (NADC), Ames, Iowa; Jan Huber, USDA/APHIS/VS, Churchton, Maryland; Fred Enright, Louisiana State University; Louisa Tabatabai, USDA/ARS/NADC; Nemat Khansari, North Dakota State University; George Lambert, USDA/ARS/NADC; L. Garry Adams, Texas A&M University; George Pugh, USDA/ARS/NADC; Shirley Halling, USDA/ARS/NADC; Paul Nicoletti, University of Florida; Edward Hoffmann, University of Florida; John Kopec, USDA/APHIS/VS, Hyattsville, Maryland; James Douglas, University of Hawaii; Marshall Phillips, USDA/ARS/NADC.

Dr. John Gorham explained that OAB has received 3 requests for guidance on procedures on the safe conduct of research on bovine brucellosis. He stated that the purpose of this meeting was to provide a background of information, to answer questions and invite recommendations from attendees, and to gather information helpful to the committee in formulating its recommendation to the ABRAC regarding confinement procedures for research with live recombinant Brucella abortus in large animals.

Dr. Gorham briefly summarized the responsibilities and functions of ABRAC and called attention to a handout he prepared if additional information was needed. He described the membership and scientific disciplines represented on ABRAC. Dr. Gorham also discussed the membership and function of the Confinement Working Group to whom this matter was referred by ABRAC.

Mr. Manuel Barbeito explained that the National Institutes of Health has been in the forefront of the establishment of guidelines for the conduct of recombinant DNA research. He briefly discussed those guidelines as they are described in the Federal Register 51, No. 88, May 7, 1986. He also discussed the proposed Appendices P & Q of the National Institutes of Health (NIH) Guidelines dealing with research on plants and animals conducted outside a laboratory. He also stressed the importance of assuring compliance with other Federal (e.g., Department of Transportation, APHIS), State and local requirements on biotechnology research.

Dr. Phillip O'Berry addressed the September 6 draft of the ABRAC guidelines and the handbook and what they will include. He indicated the handbook will be designed to complement the guidelines.

Dr. George Shibley described APHIS' responsibilities and how the agency operates. He gave information on obtaining permits and told about the different kinds of permits that are used. He indicated that APHIS operates on a case-by-case basis.

Dr. Gorham opened the floor to comments. Dr. Shirley Halling asked if there were any Brucella species now listed as nonvirulent. Dr. Shibley answered that if she knew of any she considered to be nonvirulent and she had data to support it, that would be acceptable. He indicated that an investigator might encounter a problem in the immunological challenge.

Dr. Jim Douglas stated the NIH Guidelines say that all Brucella are Class-3 organisms. He indicated there is no evidence that Brucella neotomae causes disease and questioned why it was listed as a Class-3 organism. He stated that he conducted his research with acetone killed Brucella.

Mr. Barbeito presented information about the health policy within the Department of Defense and Centers for Disease Control (CDC). He indicated that immunocompromised individuals are not allowed in a research laboratory where hazardous agents are used. This applies to both pathogenic agents or toxic compounds. He added that individuals must be immunized if a vaccine is available. This applies to both military and civilian personnel.

Dr. Edward Hoffmann asked about the documented cases of brucellosis. Mr. Barbeito said the lab acquired illnesses would have been from lab experiments rather than field experiments or exposure. He also said public health risk classification is based on what has been the experience of the infectivity of the agent and severity of the disease.

Dr. Shirley Halling asked if Brucella abortus was classified as Class-3 on the basis of concern for human health or animal health. Dr. Shibley and Mr. Barbeito expressed concern about the safety hazards associated with using a virulent strain of Brucella abortus as the challenge strain in a cattle experiment. They indicated that the entire experiment should be considered when confinement level is determined.

Dr. Paul Nicoletti added that he thought the data on Strain 19 are very clear. In his view, people get Strain 19 when they inject it and they don't get it any other way. He said we have 40-50 years of experience with this and he didn't see what additional data we need for Strain 19.

Dr. Garry Adams presented some guidelines for evaluation of Brucella vaccines. He presented specific proposals for testing vaccines outside of BL-3N containment facilities (Attachment 1). He said these are recommended guidelines for
evaluation of brucellosis vaccines either live or inactivated, developed by recombinant DNA or other methods for testing of efficacy by virulent challenge. This is a combination of BL-1N, BL-2N and BL-3N.

Dr. Adams mentioned that over 2,100 cattle have been documented to be challenged with Strain 2308 and there has not been one documented case of

Strain 2308 escaping and infecting any other cattle. He proposed to do this outdoors with the kind of confinement described in Attachment 1. The proposed procedures include measures such as sentinels, which are not part of the regulations, but he believed this to be a very good safeguard.

Dr. Gorham said Dr. Adams had some good arguments and had outlined them very well. Mr. Barbeito recommended submitting the arguments for review by the ABRAC.

Dr. O'Berry thanked everyone for attending and for their participation. Dr. Gorham adjourned the meeting at 3:56 p.m.

Janet Herrick

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November 15, 1988

Recommended Guidelines for Evaluation of Brucellosis Vaccines (Live or Inactivated) Developed through rDNA or other Methods with Testing of Efficacy by Virulent Challenge Under an Optimized Combination of BL1N, BL2N, BL3N requirements.

1. Containment area will be double fenced with one locked and restricted entrance to avoid accidental release or theft.

2. Containment area will be monitored frequently, at least four times daily.

3. All liquid and solid wastes will be collected in a retention pond, no greater than 3 ft deep with large surface area, held for 60 days, and cultured for *Brucella* prior to release.

4. The animal containment area will comply with Federal Law and animal care requirements.

5. Biohazard warning signs and special requirements for entry will be posted at all doors or gates to animal work area.

6. The Biohazard warning sign will list the name and address of laboratory director, infectious agents and animals involved.

7. The animal containment areas will be double fenced, i.e. primary and secondary barriers, constructed of steel tubing with impervious concrete floors, sheet steel ventilated sheds for ease of cleaning and disinfection.

8. Minimization of aerosols in the contaminated areas will be employed at all times.

9. Animals of any species not involved in the experiment will be disallowed in contaminated work areas.

10. Facilities, including laboratories and animal containments, will be subject to unannounced local, state and federal inspection prior and during experimentation.

11. In the case of abortion induced by *B. abortus*, the placenta and/or fetus will be carefully double contained and the site disinfected with 4% formalin.

12. Naive, non-immune susceptible reproducing sentinel cows will be stationed down-stream and/or adjacent to the double-fenced animal containment areas; however, other than these sentinels, no other cattle will have adjacent access.

13. Permanently mark (tattoo) all animals.

14. At the completion of the experiment, animals inoculated with *killed* products will be either: (a) euthanatized for necropsy and cremated, or (b) slaughtered at establishments subject to Federal Meat Inspection upon approval by the USDA/FSIS.

15. At the completion of the experiment, animals inoculated with *live* rDNA or otherwise derived products will be euthanatized for necropsy and cremation.

16. In regard to live rDNA derived *Brucella abortus* or otherwise developed vaccines, these vaccines will be evaluated in mice and/or small ruminants under BL3N conditions for fate of organism, shedding, pathogenicity, and/or efficacy before evaluations in cattle in outdoor controlled containment will begin.

17. Persons less than 18 years will not be employed.

18. Persons in containment work area will wash their hands after any contact with animals or materials involving organisms.

19. Eating, smoking, drinking, mouth pipetting and cosmetics application will not be permitted in work areas.

20. Policies, protocols and procedures for handling contaminated animals and materials will be published and presented to all laboratory workers who will be subsequently given a written examination to insure their comprehension of the safety procedures.

21. Protective clothing - lab coats, overalls, smocks will be worn in laboratory and animal work areas.

22. Skin and mucous membranes will be protected against exposure to the agent by wearing protective gloves, goggles and molded surgical masks when handling animals or contaminated materials.

23. Any accidental exposure will be reported in writing immediately to the lab director for medical consultation and treatment where requrired.

24. All laboratory personnel will have their serum samples collected at the initiation of employment and quarterly thereafter for serologic surveillance. Serum samples will be maintained as a historical human serum bank.

25. Personnel will shower when leaving the facility.

26. In order to avoid self-inoculation, use of hypodermic needles only with leur-lock syringes and sealed septum vials will be limited to only when absolutely required, e.g. inoculation, sample collection. All sharp objects will be placed in puncture-resistant containers before autoclaving.

27. Samples collected in the animal containment areas will be transported in sealed durable containers inside sealed durable rigid containers which are disinfected externally.

28. Contaminated materials will be placed in leakproof durable containers for autoclaving or transport to incineration.

29. All experimental protocols must have approval of the following local committees before initiation: IBC, Committee on Infectious Biohazards, University Laboratory Animal Care Committee, Laboratory Animal Resource and Research Committee.

Comments and Rationale

General:

1. Guidelines and regulations should be written to *facilitate* research and development while protecting the environment.

2. Guidelines for developing and testing biologics should be clearly written to avoid confusion in obtaining approval.

3. Requirements for approval to evaluate biologics should be clearly stated to avoid and eliminate overlapping jurisdiction at local, state and federal levels, i.e., IBC, NIH, USDA/APHIS/Veterinary Biologics, USDA/OAB/ABRAC.

4. Delegate the authority having jurisdiction first to the local IBC, then to *either* USDA/OAB/ABRAC *or* USDA/APHIS/Vet Biologics or NIH but *not* all three.

5. Approaches to improved biologics has changed significantly, but the products are *not* significantly different from those produced by conventional methods, in fact virtually all new biologics are better characterized and safer than the products they replace.

6. Questions pertaining to new biologics should be focused on the safety, efficacy and intended use not on the methods employed in their development or production.

7. The approach to meet the containment needs should be pragmatic because of the high costs and time involved.

Relevant Data:

1. In the case of mammalian brucellosis, there is no evidence of arthropod transmission.

2. In the case of bovine brucellosis, the pregnant *Brucella abortus* infected cow is the *only* major factor in disease transmission to other cattle and man.

3. *Brucella abortus* has been documented to only survive *not* replicate outside a narrow host range.

4. The ID_{50} of *B. abortus* for cattle has been estimated in publications to be $\approx 1 \times 10^4$ cfu.

5. Man has been demonstrated to have the following decreasing susceptibility to *Brucella spp*: *B. melitensis* > *B. suis* > *B. abortus* and man is less susceptible to *B. abortus* than cattle are.

6. Some published *B. abortus* survival studies: See enclosed Table 14-4.

7. Currently under Federal law, cattle infected with field strains of *Brucella abortus* are sold in markets and slaughtered in USDA/FSIS sanctioned abattoirs.

8. Human brucellosiscaused by *Brucella abortus* can be chemotherapeutically treated effectively with antibiotic regimen.

9. NIH classifies all Brucellae as Class 3 including *Brucella abortus* S19 which is a USDA/APHIS/VS licensed and widely disseminated vaccine, i.e. under this classification system. all S19 vaccine would have to be produced under BL3N confinement.

10. In over 2360 cattle, bison, goats, sheep and/or elk experimentally challenged with prototype virulent field strain *Brucella abortus* S2308, no confirmed evidence of transmission to any other domestic livestock species has occurred from 1971 through 1988.

In Case of Failure:

1. If a barrier fails, what are the acceptable limits of failure? Answer: Seroconversion but no infection of sentinels.

2. How will failure be measured? Answer: Seroconversion, clinical signs and bacteriologic culture of sentinels.

3. What procedures will be used to correct emergency situations? Answer: Seroconversion test, euthanasia and cremation.

4. What is the weakest link in the containment? Answer: Accidental release of exposed pregnant cows; Prevention - Secure containment to prevent escape or release.

5. What is the cost of maintaining barriers versus cost of correction in case of failure? Serologic surveillance and slaughter in restricted zones may well be more cost effective and efficient than maintaining barriers, but *both* are *essential.*

Proposed Containment:

1. It is *not* logical to prevent the evaluation of new killed or live *Brucella abortus* vaccines by virulent challenge in endemic zones where not only *containment*, but *isolation* to prevent accidental entry of field strain *Brucella abortus* is of equal importance.

2. With the enclosed proposed controlled containment management system, the effects of dilution in air or water plus the effects of temperature, pH, and sunlight significantly reduce the potential for transmission below $\approx 1 \times 10^{4}$ cfu ID_{50} threshold for cattle, i.e. *Brucella spp* have rarely been documented to be transmitted by inert objects.

3. We propose that the enclosed controlled containment management system will provide more than an adequate envelope or barrier around *Brucella abortus* live rDNA or killed vaccination/challenge experiments to prevent accidental exposure to man, animals, or environment, because we have:

   (a) Established management protocols
   (b) Isolated *Brucella abortus* at the source
   (c) Reduced and minimized risk of exposure
   (d) Increased distance from other cattle through dilution and space
   (e) Built in redundancy through primary and secondary barriers with sentinels to monitor accidental exposure
   (f) Documented experimental animals and treatments
   (g) Documented monitoring and surveillance protocols for laboratory workers in case of accidental exposure
   (h) Identified issues related to facility location and environment.
   (i) Strategized the assessment of live rDNA vaccines in rodents and/or small ruminants under BL3N conditions for fate of organism, pathogenicity and shedding before evaluation in cattle in outdoor controlled containment areas would begin and therefore, these protocols, properly employed, will specifically prevent any implied or real negligence, which is the failure to excise due care for man, cattle and the environment.

Table 14.4. Survival times of *B. abortus* under various environmental conditions

Medium	Temperature or season	Environmental conditions	Survival time (days)	Reference
Uterine exudate	February	Placed on ground	10	Cotton. Jour. Am. Vet. Med. Assoc., 1919, *55*, 504.
Placenta, fetal organs	Winter and spring	Covered with leaves in forest	135	Cotton. Jour. Am. Vet. Med. Assoc., 1919, *55*, 504.
Milk	15 C	Milk samples from infected cows	38	Huddelson, Hasley, and Torrey. Jour. Inf. Dis., 1927, *40*, 352.
Butter			142	Carpenter and Boak. Am. Jour. Pub. Health, 1928, *18*, 743.
Cheese	4.4 C		180	Gilman, Dahlberg, and Marquardt. Jour. Dairy Sci., 1946, *29*, 71.
Grass	10-70 F, February	0.6 in. rain	6	Ky. Agr. Exp. Sta. Bull. 43, 1931, p. 14.
	60-81 F, May	Sunny	<1	Ky. Agr. Exp. Sta. Bull. 43, 1931, p. 14.
	36-70 F, November		5	Ky. Agr. Exp. Sta. Bull. 43, 1931, p. 14.
Open plate cultures	October and November	Sunny	2-3	Ky. Agr. Exp. Sta. Bull. 43, 1931, p. 14.
Water	−40 C		800	Kuzdas and Morse. Cornell Vet., 1954, *44*, 216.
	37 C, 25 C, 8 C		57	
Infected guinea pig carcass	January (Wisconsin)	Placed on ground	44	Kuzdas and Morse. Cornell Vet., 1954, *44*, 216.
	June and August (Wisconsin)	Placed on ground	1	Kuzdas and Morse. Cornell Vet., 1954, *44*, 216.
	January (Wisconsin)	Buried	29	Kuzdas and Morse. Cornell Vet., 1954, *44*, 216.
Meat and salted meat	0-20 C		65	Prost. Ann. Univ. Marie Curie—Sklodowska, Lublin, Poland, 1957, *12*, 163.
Manure pit	158 F	In tubes at bottom of pit	<4 hours	King. Jour. Am. Vet. Med. Assoc., 1957, *131*, 349.
Manure pit		In tubes at top of pit	2	King. Jour. Am. Vet. Med. Assoc., 1957, *131*, 349.
In manure	12 C		250	Plommet. Anns. Recher. Vet., 1972, *3*, 621.

Survival of *Brucella* in Sterilized and Untreated Bovine Manure and Soil at Various Temperatures

Temp. (C)	Bovine Manure		Soil	
	Sterilized	Untreated	Sterilized	Untreated
37	188 Days	0 Days	100 Days	5 Days
25	286 Days	29 Days	156 Days	29 Days
8	227 Days	385 Days	93 Days	188 Days
-3	325 Days	121 Days	52 Days	188 Days
-40	670 Days	670 Days	670 Days	670 Days

Kuzdas, C. E. and Morse, E. V. Cornell Vet.. 44:216-228 (1954).

MINUTES

AGRICULTURAL BIOTECHNOLOGY RESEARCH ADVISORY COMMITTEE
WORKING GROUP ON GUIDELINES
U.S. Department of Agriculture
Room 3109-South Building
Washington, DC
December 2, 1988

The meeting of the Agricultural Biotechnology Research Advisory Committee (ABRAC) Working Group on Guidelines was called to order on December 2, 1988, at 9:10 a. m. by Dr. Sue Tolin, Chair. The meeting was open to the public and was announced in the Federal Register.

Members of the working group in attendance were: A. David Kline, F. William Whitmore, Ronald Sederoff, George Hill, and Anne K. Vidaver. Others in attendance were: Lambert Wenner, Daniel Jones, Maryln Cordle, Eva Russnak, and Barry Stone, OAB; H. Graham Purchase, ARS; Paul Stern, University of Florida; and Frank Serdy, Monsanto Corp. There were three visitors present.

I. INTRODUCTION

Dr. Young welcomed the group and complimented them on the past six months' productive efforts. He emphasized the great need for field research guidelines in the scientific community. The next draft of the OAB Guidelines will be reviewed by ABRAC at its January 5-6, 1989, meeting. Pending ABRAC approval, the Guidelines will be distributed for review by USDA and other agencies. Following Office of Management and Budget (OMB) and Biotechnology Science Coordinating Committee (BSCC) approval, the Guidelines will be published in the Federal Register for public review and comment. The Guidelines would likely be reviewed at the March meeting of ABRAC, and a final draft is expected by June 1989.

Dr. Young added that other Federal agencies, especially the National Science Foundation (NSF) have great interest in our work. The USDA Guidelines may become the standard for other organizations involved in field testing of organisms produced through biotechnological techniques.

II. CHARGE TO THE WORKING GROUP

The November 30, 1988, draft of the Guidelines was distributed for discussion and additional changes needed prior to the January 5-6, 1989 ABRAC meeting. This draft included the OAB Draft revisions of the October 24 draft and some ABRAC comments on the October draft. Six letters of comment on the October draft were received from ABRAC members in time for distribution at this meeting. Dr. Tolin also distributed a three page-supplement which consisted of some alternative language.

III. CRITIQUE OF THE NOVEMBER 30, 1988 DRAFT GUIDELINES

The group decided to consider the Guidelines one section at a time:

Section I. Purpose.--

The November draft reflects additions made in response to ABRAC comments (1) to show the relationship of the Guidelines to Federal agency regulations and (2) to provide an "applicability" statement.

The first paragraph read as follows:

> These Guidelines are designed to specify practices and procedures for agricultural research outside the laboratory involving biotechnology in order to prevent unreasonable adverse effects on human health or managed or natural ecosystems. The Guidelines establish fundamental principles upon which many specific cases can be evaluated that transcend particular experiments and organisms.

Dr. Vidaver expressed concern with the wording of "unreasonable adverse effects" and suggested that mention of such effects may imply that agricultural research poses great risk.

Dr. Kline felt the phrase was good and suggested changing "unreasonable" to "unreasonably" to improve the grammar.

Dr. Sederoff stated that the Guidelines are intended to prevent adverse effects and are merely cautionary.

Mr. Stern explained that "unreasonable" is a term that has developed a "standard" meaning through years of court cases. It has become not only part of our law, but part of our society.

Dr. Whitmore stated that the statement of "preventing unreasonable adverse effects" is needed, even if the descriptive terms are changed.

Dr. Vidaver moved to substitute "minimize" for "prevent." Dr. Sederoff seconded and amended to remove "in order" and to insert "on" before "managed."

Dr. Purchase recommended putting terms such as, "reasonable" and "managed ecosystem" in the definitions and stated that they need to be consistent throughout the document.

The motion was not seconded.

Dr. Sederoff moved to remove "in order" and to insert "on" before "or managed ecosystems." The motion carried.

Dr. Kline suggested simply inserting a period after "evaluated." Dr. Sederoff agreed.

Dr. Purchase suggested defining "safety" or "biosafety" in the definitions and using that term throughout the Guidelines. The Group agreed that this would be appropriate, and that it would embody the concept of preventing unreasonable adverse effects on human health or on managed or natural ecosystems.

Dr. Kline moved to omit the end of the last sentence following "evaluated." The motion carried.

Dr. Sederoff called for another sentence to express the purpose of the Guidelines.

Dr. Purchase recommended adding "upon which confinement practices can be based." Sederoff so moved and the motion was seconded and carried. The second paragraph read as follows:

> When the practices and procedures of these Guidelines conflict with Federal regulatory requirements for research activities, those regulatory requirements supersede the Guidelines.

After considerable discussion over the implications of the second paragraph, Mr. Stern offered the following wording: "These Guidelines do not preclude compliance with regulatory requirements of Federal, State, or local agencies." Motion was made, seconded, and carried.

The third paragraph read as follows:

> These Guidelines apply to all research funded by USDA; experiments which are not in compliance with the Guidelines will be subject to loss of funding. Institutions conducting biotechnological research outside the laboratory that is not funded by USDA are encouraged to comply with the Guidelines on voluntary basis.

Dr. Jones, reflecting the advice of USDA's General Counsel, explained that, if the Guidelines contain sanctions for nonconformity (e. g., loss of funding) they must become formal regulations through the formal Federal regulations process. He indicated that OGC suggested the option of deleting these sanctions.

Dr. Whitmore suggested removing the phrase, "will be subject to loss of funding."

Dr. Tolin expressed ABRAC's intent to guide, not to regulate.

Dr. Serdy inquired whether the USDA scope and purpose document for OAB covers this.

Dr. Purchase said legislation authorizing CSRS grants will require compliance with Guidelines.

Dr. Sederoff favored modifying the last sentence to emphasize that compliance with Guidelines helps insure safety. Others felt this was unnecessary.

Dr. Serdy commented that industry is already heavily regulated. Advocate groups could use these Guidelines as a basis for unreasonable court action if the last paragraph requiring compliance is left in.

Mr. Stern questioned whether the provision encouraging compliance by private institutions would provide standing to sue those institutions if they did not comply with the Guidelines. The Group also emphasized in discussion that practices under the Guidelines would be quite dependant upon individual researchers' designs. When an individual's methods include safety protocols not specified by the current Guidelines, amendment to the Guidelines is in order so that future experiments could utilize the new protocol. The Guidelines are intended to be receptive to changes to reflect the current

state of knowledge and practice. Enforcement will more than likely be carried out by others; it may not be a primary concern of ABRAC.

Dr. Hill moved to remove the second sentence in the third paragraph, and to move it to another portion of the Guidelines. The motion was defeated.

Dr. Tolin observed that, by consensus, the last half of the first sentence after USDA mandating loss of funding for noncompliance will be omitted. No objections were voiced.

Dr. Sederoff moved to add "to assure safety," to the end of the second sentence. The motion carried.

Dr. Tolin stated that following a discussion from Dr. Purchase on the status of the Handbook, the order of discussion of remaining sections of the Guidelines would be V, VI, VII, and VIII followed by II and IV, and, if there was time, III. This choice was made to assure adequate times for sections of the Guidelines which had previously had little open discussion, and to provide Dr. Purchase time on the agenda before his departure.

Status of the "Handbook":

The Chair invited Dr. Purchase to review the status of the Handbook at this time. The Handbook is now called, "Introduction to Field Testing." The chapters have been reordered, beginning with the responsibilities of the PI and progressing onward to institutions, USDA, etc. Some sections are being shortened (ethics, social issues, etc.), and others have been expanded (e. g., requirements of other agencies). The document will be reconciled with the Guidelines when the latter are completed, and it will be edited for consistency, clarity, etc.

Section V. Roles and Responsibilities:

Dr. Tolin pointed out changes made to reflect ABRAC discussions at the September meeting. The direction to report accidents or significant problems to OAB within 15 days (instead of 30 days) was changed in 3 places (V-A-7, V-B-3-b, and V-C-3).

Dr. Hill moved to insert "promptly" in V-A-7 instead of "within 30 days" and to insert "implementation of" before "Guidelines." Make these changes also in V-B-3-b and V-C-3. These changes were approved by consensus.

Dr. Tolin suggested changing the first sentence of V-A-7 and 8 to read: "Assure that the IBC reports..." She offered a change for V-C-4 to read: "Report to the IBC as soon as it is recognized so that the IBC can report to OAB within 15 days of recognition." This change was approved by consensus

Mr. Stern suggested "immediately" instead of "as soon as possible" to assure that accidents were reported in time to allow the most effective remedial actions. The Group felt that in a research situation it was not always possible to report "immediately," and that "as soon as it is recognized" was the most appropriate language.

The Group was concerned about too many different responsible parties for reporting the same information to OAB, but felt the changes remedied this problem. The PI reports to the IBC, who in turn reports to OAB. The institution assumes that these steps are done.

Section V-A-6:

Dr. Purchase offered language to achieve parallel construction in this section: substitute for the last two lines, unless it is confidential business information or, unless its disclosure is prohibited by state or Federal law." The Motion was approved by consensus.

Section V-B-2-b:

"Be involved with" was offered as a replacement for "engaged" in two places. This was approved by consensus.

Section V-B-1:

Mr. Stern related ABRAC comments that the Guidelines should emphasize that existing IBCs might be appropriate to use; e. g., IBCs established under other agency procedures.

Dr. Tolin offered the following language: "An existing IBC may be expanded as necessary to provide the expertise required to meet the requirements of and perform functions for compliance with the USDA Guidelines." The motion was approved by consensus.

Section V-D-3:

Mr. Stern pointed out an ABRAC comment on the need to modify the second sentence by deleting "all" and changing "should" to "can." The motion was approved by consensus.

Section VI: Protection of Proprietary Data.

Dr. Jones mentioned that the Handbook will provide guidance on confidential business information (CBI) protection; few commenters expressed concern on this. He also noted that OAB's proposed USDA regulation on CBI was rejected by OMB, and OAB has drafted a response to OMB. No changes in this section were recommended by the Working Group.

Section VII: Amendment Procedures.

Dr. Tolin noted that, the Guidelines should be revised to describe the process for handling requests for amendments.

Dr. Serdy asked whether changes would have to go through the same approval process as these Guidelines.

Dr. Tolin stated that Section VII would expand with the help of Paul Stern and Dan Jones of OAB to provide more details. The Group felt it would be important to include a provision in the Guidelines for prompt replies to the requesters.

Section VIII: Definitions.

Dr. Tolin explained that the list of defined terms in the draft does not include those terms which are not used in the Guidelines. The Group agreed that this omission was desirable.

Dr. Whitmore recommended inserting "habitats and their interactions" in definition VIII-A-7. Dr. Tolin agreed.

Dr. Vidaver questioned the utility of the definition of organism (VIII-A-8). Following discussion in which all agreed that biologists have a general agreement on a definition of organisms. The definition was deleted by consensus.

In accordance with the earlier discussion of the Group under Section I, a definition of "safety" was presented by Dr. Tolin, which would be section VIII-A-9: "Safety" refers to the prevention of unreasonable adverse effects on human health or on managed or natural ecosystems. A "safe" experiment is one which is conducted using practices designed to assure safety.

Section II: Classification of Organisms

Dr. Tolin explained how a subcommittee of this working group proposed the revised new content of Section II at the September meeting. Classification of organisms was largely accepted, but the nature of modifications with DNA need more discussion.

Dr. Whitmore noted a need to change the wording of "unreasonable adverse effects" to "safety" throughout the Guidelines beginning on p. 2, to be consistent with the previous discussion. Dr. Tolin asked that this be done in the next draft.

Dr. Tolin expressed the need to review the statuses in Section II-A; A Status 5 has been added in this draft, and some organisms may still be misclassified. The Group insisted on the need to retain both types of modifications and classes of organisms. Considerable discussion followed on the proper scope of the Guidelines to express on p. 4, section II-B-I. The emerging consensus was that broad scope is appropriate for the USDA Guidelines, and that this scope should be attained by means other than redefining biotechnology.

Dr. Kline asked whether "deletions" should be included in this section in the scope. Dr. Tolin explained that the Working Group should consider itself constrained by the definition as agreed to by ABRAC by a 6-3-1 vote and that major changes cannot be made until ABRAC reconvenes. Section IV is intended to address the change in status as the result of genetic modification, but scope and extent belong in Section II.

Dr. Whitmore suggested changing the third sentence of section II-B-1 to, "These guidelines do not apply to research in biotechnology that is limited to study." The group agreed to this change by consensus.

Dr. Vidaver suggested inserting "or manipulation" after "introduction" in the first sentence of II-B-1. The group agreed to this change by consensus.

Dr. Sederoff noted that DNA can be manipulated to differ from that which occurs naturally. He said that the distinction between what does and does not occur naturally is the basis for our establishing categories, but this distinction has resulted in ambiguous interpretations. The intent was that a change that would occur naturally, including changes with an organism's own DNA, would be "natural" changes have no effect on the status of the organism. Dr. Tolin felt this to be an issue to present to ABRAC.

It was agreed that categories II-B-3-a and b in the October 24 draft, can be combined and that modifications solely from same-species DNA or RNA should be added. Subtitles could be used to describe all three possible types of modifications presented by Dr. Sederoff.

II-8-3 Type 1:

-- modifications that result in organisms that (1) contain simple deletions or point mutations that are essentially equivalent to those modifications that are likely to occur naturally.

-- (2) contain multiple deletions or complex genomic rearrangements which are unlikely to occur naturally,

-- (3) contain added nucleic acid solely of the same species except for sequences known to produce or induce highly hazardous traits, such as toxins.

Type II: Genetic modifications that result in organisms containing insertions of nucleic acid from different species that result in:

(1) no change, (2) known, with no or low hazard, (3) unknown, but not expected to be severe.

Dr. Sederoff outlined the following additional points:

Issues to address:

-spliced and chimeric genes
-functional versus nonfunctional added sequences
-genetic distance between species--when great distances are involved, added genes usually are nonfunctional
-hazard of foreign genes should be based on intrinsic function
-coding versus noncoding sequences
-donor organism and its importance

Real concerns include using genes coding for really hazardous products.

Type II genetic modifications should include:

-most functional and nonfunctional genes
-most donor organisms
-most spliced genes

Type III Genetic modifications should be those that result in a known organism with a high hazard.

Dr. Tolin expressed the view that, with increased knowledge of organisms, some Type III could be judged to be Type II modifications. Initial experiments would require a higher confinement level for Type III modifications than for the unmodified organism.

Dr. Sederoff concluded that there would be 12 possibilities based on 4 types of organisms and 3 types of genetic modifications. A 4 by 3 matrix could be developed to cover each possibility for confinement.

Dr. Sederoff agreed to develop his scheme further and to present it to ABRAC as a useful approach. The group concurred and encouraged his effort.

To accommodate this scheme, Dr. Tolin suggested new wording for the next to the last sentence of section II-B-2: "This categorization provides a framework for assessing the likelihood of such modifications for changing the status of experimental organisms."

Dr. Vidaver pointed out the need to distinguish the original from the modified organism.

Section IV. Conduct and Review of Experiments:

Dr. Tolin noted that the consensus seemed to be that the status of an nonmodified organism times the Type of modification would equal the category of modified organism. She said the Principal Investigator should describe the appropriate practice to meet the confinement level. The category of an organism, the experiment to be conducted, and the confinement level recommended determine the class of experiment and review requirements, which should be described in the Guidelines in Section IV. Accordingly, the last sentence in Section II-B-2 should be expanded, and the point conveyed in section IV.

As to review level, Drs. Tolin and Sederoff agreed that, at a minimum, the IBC should receive all field testing proposals. If an experiment is not covered by the Guidelines, the proposal would go to ABRAC. Initially all proposals would probably, in reality, go to ABRAC or to a regulatory agency for approval. This process will have to be tested with experiments to see how well it works.

Ms. Cordle suggested we might do as NIH did and use the Guidelines on a test basis.

Dr. Tolin stated the consensus was to include that "initially everything must be reviewed by ABRAC or a regulatory agency." With time and experience, classes of experiments can be assigned for IBC review only. The group agreed

to accept the 4 recommended confinement levels for categories of organisms as listed on p. 21 of the October 24 draft (IV-A) as a starting point. The PI should design the experiment to meet the appropriate level, and the IBC should confirm or modify the proposal before the experiment is initiated. The group agreed these points should be stated in Section IV.

Dr. Sederoff moved that "the PI should determine the category of the experiment" to be inserted in the opening paragraph of Section IV. The motion carried.

Dr. Tolin suggested that, in IV-B, two levels could actually be used: IBC review, and IBC and ABRAC review. She proposed the following changes:

IV-B-1 - Exempt Experiments: Currently no experiments fall in this category, but some could be added.

IV-B-2 - Experiments that should be submitted to IBC: none currently fell in this category, but some could be added.

IV-B-3 - Experiments that should be approved by IBC prior to initiation could be those that are Class 1,2, or 3.

IV-B-4 - Experiments that should be approved by the IBC, reviewed by ABRAC, and approved by USDA. These could be those that are in Class 4, and perhaps Class 3.

Dr. Tolin suggested further that the following be added to Section IV:

> "The PI or IBC can request ABRAC to review selected confinement level descriptions for particular categories of organisms."

The group agreed to present this type of scheme to ABRAC and reminded themselves that ABRAC will only recommend--not approve--experiments conducted under certain confinement practices. This could be done by phone or letter to the Director of OAB, who may present this to ABRAC. OAB would develop an information base from these experiences.

Section II-A: Classification of Organisms

Mr. Stern reintroduced the statuses in Section II-A for discussion. The statuses presented in the November 30, 1988 draft are adapted from the working group deliberations at the September ABRAC meeting.

Dr. Vidaver explained that the insertion of "little or no" in place of "no" for status 1 would make it more scientifically defensible and that "based on extensive biological knowledge" should be stricken because its exact meaning or implication is vague at this time. The group agreed.

Dr. Tolin expressed the desire to divide statuses 1 and 2 into "a" and "b" sections, as in 3 and 4 and to insert "or" in status 1 and 2. It was agreed to insert "or" before each clause in Statuses 1&2.

Dr. Sederoff was concerned about the use of "unreasonable" in status levels 1,2, and 3. It was agreed to delete this word. He also added that there is a need to insert, up front, the key difference in the statuses and make their distinctions science-based. This should be precise, so that the 5 status levels are distinct.

Dr. Tolin suggested that a sentence on how much is known could be in the preamble to the section.

IV. **ADJOURNMENT**

The meeting was adjourned at 5:15 p.m., December 2, 1988

FOR/ BERT WENNER
Rapporteur

PAUL STERN
Rapporteur

SUE TOLIN
Chair, Guidelines Working Group

* U. S. GOVERNMENT PRINTING OFFICE:1989-241-867:00218/C5R5